This Month in Genetics

Kathryn B. Garber[1,*]

Incidental, or Unhelpful?

Many of the genes considered to include actionable incidental findings, according to recommendations by the American College of Medical Genetics and Genomics, are cardiac genes implicated in arrhythmia and sudden cardiac death. Researchers classically seek variation in these genes to explain overt cardiac phenotypes in patients, but by definition, an incidental finding is one that does not explain the referring diagnosis. Because of this dichotomy, van Driest et al. used an unselected adult cohort to assess the presence of relevant cardiac phenotypes, as gleaned from electronic medical records, in individuals with variation in two of these actionable genes, *KCNH2* and *SCN5A*. The group with a putative pathogenic variant in either gene did not have increased risk of arrhythmia or a relevant ECG finding, leading the authors to question whether patients should be notified of incidental findings in these genes.

van Driest et al. (2015). Association of arrhythmia-related genetic variants with phenotypes documented in electronic medical records. JAMA 315, *47–57*.

You Are What Your Father Eats

Paternal nutrition can influence the metabolism of offspring, but the mechanism for this epigenetic phenomenon has been murky. Rather than the classic epigenetic marks of DNA methylation and histone modifications, two recent papers in *Science* instead suggest a role for tRNA fragments in the impact of paternal diet on their offspring. Both groups found that the diet of male mice influences expression of tRNA fragments in sperm. Chen et al. recapitulated the intergenerational effects on metabolism by isolating these RNA fragments and injecting them into oocytes. Sharma *et al.* found that the fragments are likely to be delivered to maturing sperm via vesicles that fuse with sperm as they transit the epididymis. Once inside an embryo, the tRNA fragments impact gene expression, an outcome that might ultimately alter metabolism in the offspring.

Sharma et al. (2015). Biogenesis and function of tRNA fragments during sperm maturation and fertilization in mammals. Science. Published online December 31, 2015. 10.1126/science.aad6780.

Chen et al. (2015). Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science. Published online December 31, 2015. 10.1126/science.aad7977.

All in the Family

Genetic counselors have to rely on empirical risk estimates to predict recurrence of apparently de novo autosomal-dominant disorders. Although mosaicism in a parent is thought to be relatively unlikely, the potential means a counselor never says "never again" to these families. To look at new mutations on a genome scale, Rahbari *et al.* assessed whole-genome sequences of families with multiple children and found that mosaicism is actually fairly common in the germline; it accounts for nearly 4% of mutations and explains how 1.3% of apparently de novo variants could be shared by siblings, despite a lack of heterozygosity for the variant in either parent. The presumed parental somatic mosaicism for these variants was confirmed in six of ten cases via deep sequencing of parental samples. Beyond this exploration of mosaicism, Rahbari et al. use their data to confirm the paternal age effect on de novo mutation rates and also to suggest that the magnitude of this age effect differs between families. Although fewer new mutations arise in the female germline, the spectrum in oocytes is similar to what occurs in sperm.

Rahbari et al. (2015). Timing, rates, and spectra of human germline mutation. Nature Genetics. Published online December 14, 2015. 10.1038/ng.3469.

ExACtly What We Need

The Exome Aggregation Consortium (ExAC) data, which encompasses exome sequences from more than 60,000 individuals from around the world, became available just over a year ago. It quickly became a major resource of population data to facilitate variant interpretation by clinical genetic testing labs. A group at Integrated Genetics recently performed an analysis that supports the use of ExAC as a control cohort for this purpose. The group selected curated pathogenic or likely pathogenic variation in a variety of genes and determined the allele frequency of each in ExAC. Next, they compared these values to their estimated maximal pathogenic allele frequency for each gene. Of nearly 900 variants, only three exceeded the estimated maximal pathogenic allele frequency, and the classification of each was downgraded from pathogenic. Next, the group looked more globally at the ExAC-derived allele frequencies for variation in these genes and found that the majority of variation that

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
http://dx.doi.org/10.1016/j.ajhg.2016.01.001.

exceeded the maximal pathogenic allele frequency was already classified as benign or likely benign in their system. One exception highlights a problem with the use of ExAC data for variant assessment. Nine variants purportedly in *PMS2* exceeded the expected pathogenic allele frequency for Lynch syndrome. A pseudogene for *PMS2* makes it hard to map next-generation sequencing reads to the true genomic location. With the ExAC data, one cannot rule out pseudogene interference in variation assigned to *PMS2*, so the authors suggest a conservative use of ExAC for this gene and others with problematic pseudogenes.

Song et al. (2015). Exploring the landscape of pathogenic genetic variation in the ExAC population database: insights of relevance to variant classification. Genetics in Medicine. Published online December 17, 2015. 10.1038/gim.2015.180.

Getting Left Out

Micronuclei sometimes form when a chromosome lags behind the rest during mitosis; the chromosome is kept separate from the nucleus in this structure and can become damaged. In cancer cells, micronuclei have been implicated in the mechanism of chromosome shattering called chromothripsis, and these heavily damaged chromosomes are ultimately reincorporated into the nucleus. Rather than studying cancer cells, Vázquez-Diez et al. monitored micronuclei in early mouse embryos. From the 16-cell stage onward, mouse embryos commonly have micronuclei-containing cells. What is strikingly different from cancer cells is that these chromosomes are not reincorporated into the nucleus; instead, the micronuclei fail to interact with the spindle apparatus and, as a result, are transferred passively to only one of the two daughter cells when the cell divides. This suggests a mechanism to explain the mosaic aneuploidy observed in many preimplantation embryos. At the same time, ensuring the micronuclei are left out of the nucleus might protect embryos from chromothripsis.

Vázquez-Diez et al. (2016). Micronucleus formation causes perpetual unilateral chromosome inheritance in mouse embryos. Proc. Natl. Acad. Sci. 113, *626–631.*

This Month in Our Sister Journal

Hitting the Bullseye

Positive hits from genome-wide association studies are simply a first step to understanding genetic traits of interest. Correlations between genetic variation mean that these associations implicate a genomic region rather than a specific variant, and it can be difficult to know on which specific variant to focus further efforts. Stell and Sabatti propose an approach that lets them use known information about a variant's function, to account for contributions of multiple genes, and to use information from multiple phenotypes and multiple variants in the same gene. They illustrate the utility of their approach with data from a resequencing study.

Stell and Sabatti (2015). Genetic variant selection Learning across traits and sites. Genetics. Published online December 17, 2015. 10.1534/genetics.115.184572.